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How can imported monkeypox break the borders? A rapid systematic review

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ABSTRACT

Background: Monkeypox was designated as an emerging illness in 2018 by the World Health Organization Research and Development Blueprint, necessitating expedited research, development, and public health action. In this review, we aim to shed the light on the imported cases of monkeypox in attempt to prevent the further spread of the disease. Methodology

Abbreviations: WHO, World Health Organization; MSM, Men Who have sex with men; R0, R naught; JBI, Joanna Briggs Institute; NOS, Newcastle-Ottawa Scale; WOS, Web of Science; HIV, Human immunodeficiency virus; UK, United Kingdom; USA, United States of America; PCR, Polymerase chain reaction.

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Nigeria
Imported infection
Disease surveillance

An electronic search in the relevant database (Web of Science, PubMed Medline, PubMed Central, Google scholar, and Embase) was conducted to identify eligible articles. In addition to searching the grey literature, manual searching was carried out using the reference chain approach.

Results: A total of 1886 articles were retrieved using the search strategy with 21 studies included in the systematic review. A total of 113 cases of imported monkeypox were confirmed worldwide. Nineteen patients mentioned a travel history from Nigeria, thirty-eight infected cases had travel destinations from Europe, fifty-four cases traveled from European countries such as; Spain, France, and the Netherlands, one case from Portugal, and another one from the United Kingdom (UK). All reported clades of the virus were West African clade. Nine studies showed the source of infection was sexual contact, especially with male partners. Six studies mentioned the cause of infection was contact with an individual with monkeypox symptoms. Two studies considered cases due to acquired nosocomial infection. Ingestion of barbecued bushmeat was the source of infection in three studies and rodent carcasses were the source of infection in the other two studies.

Conclusion: The development of functioning surveillance systems and point-of-entry screening is essential for worldwide health security. This necessitates ongoing training of front-line health professionals to ensure that imported monkeypox is properly diagnosed and managed. In addition, implementing effective health communication about monkeypox prevention and control is mandatory to help individuals to make informed decisions to protect their own and their communities' health.

1. Background

Monkeypox is a re-emerging rare zoonotic infectious disease. The monkeypox virus is related to the orthopoxviral family and poxviridae genus. This virus's natural hosts are vertebrates and arthropods. Monkeypox was first identified in 1958 when two outbreaks occurred in research-held monkeys that started exhibiting symptoms of a pox-like illness [1]. In 1970, the disease was first confirmed in humans, by a child suspected of having smallpox in the Democratic Republic of Congo. In 2003, the first outbreak of monkeypox outside of Africa was reported in the United States of America (USA) [1,2].

Monkeypox was designated as an emerging illness in 2018 by the World Health Organization (WHO) Research and Development Blueprint, necessitating expedited research, development, and public health action [3]. The growing global monkeypox outbreak was deemed a Public Health Emergency of International Concern on July 23, 2022, by WHO Director-General. As of 10 November 2022, a total of 79 483 confirmed cases were reported with 49 deaths reported in 110 countries. The number of new cases reported increased by 2.5% in week 44 compared with week 43. Of note, 86.3% of cases were reported in 10 countries: the USA, Brazil, Spain, France, The United Kingdom (UK), Germany, Colombia, Peru, Mexico, and Canada. The highest prevalence was reported in regions of the Americas and Europe [4]. People under the age of 40 conform to the majority of confirmed cases of monkeypox, with a median age of 31 years [5]. This group was only born after the smallpox vaccination campaign was stopped, further emphasizing the absence of cross-protective immunity [5,6].

The monkeypox virus is divided into two separate genetic clades, the Central African (Congo Basin) clade, and the West African clade. The Central African clade was thought to be more contagious and to produce more severe illness. Moreover, the Central African clade's mortality rate was approximately triple that of the West African clade [7]. Of note, The majority of cases reported outside West and Central Africa are linked to the imported cases [7]. However, recently, several monkeypox outbreaks have been reported outside those endemic countries and have even gradually caused worldwide outbreaks without known epidemiological links to West or Central Africa [8].

Monkeypox can be spread by both infected humans and animals. Nevertheless, considering the known illness characteristics of the infected patients and the obvious localized or generalized skin lesions, silent human-to-human transmission from asymptomatic patients appears unlikely. [9,10] Additionally, a significant portion of these male-to-male sexual (MSM) partners and bisexual men have had monkeypox viral infections, raising the risk of sexual transmission [9]. It is interesting to note that there is a cross-protectivity of the smallpox vaccination against smallpox and monkeypox virus infection due to the high nucleotide identity (96.3%) in the central region between these two viruses [9].

R naught (R0) is known as the reproduction ratio, which is a way of defining the disease's degree of transmissibility. According to an epidemiological modeling study, the monkeypox R0 value ranges from 1.10 to 2.40 in nations with minimal contact with orthopoxvirus species [11]. In circumstances of imported human or animal cases, this value implies that a monkeypox pandemic is about to break out [5,12]. A person who is infected must take particular precautions to socially isolate and quarantine themselves due to the virus's ability to spread [3]. So, several steps must be taken to stop the viral transmission to halt the monkeypox outbreak. These steps include the creation of rapid diagnostic assays with high sensitivity and specificity, active surveillance and monitoring systems, and the potential use of the smallpox vaccine for post-exposure prophylaxis of close contacts [8,13].

In this review, we aim to shed the light on the imported cases of monkeypox to prevent the further spread of the disease. This would help policymakers and stakeholders to implement more stringent public health and social measures for better epidemic control.

2. Methods

The current study was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, [14] and the Cochrane Handbook of Systematic Review and Meta-Analysis [15]. The protocol of the study was registered in the

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international prospective register of systematic reviews (PROSPERO) [CRD42022351486].

2.1. Studied outcomes

Primary objective:

- Trace the imported cases of monkeypox (source and destination) to prevent the further spread of the disease.

Secondary objectives:

- Identify the mode of transmission among imported cases.
- Highlight the clade monkeypox.
- Describe signs and symptoms among imported cases and secondary cases.
- Address the control and preventive measures adopted by different health authorities that received the imported cases.

2.2. Search strategy

An electronic search in the relevant database (Web of Science (WOS), PubMed Medline, PubMed Central, Google scholar, and Embase) was conducted by two authors to identify eligible articles. The keywords were included according to the different search platforms (Supplementary File). The database search ended on August 5, 2022. In addition to searching the grey literature, manual searching was carried out using the reference chain approach. It included searching for references from eligible articles, citation tracking, and looking at related articles for eligible articles. The eligibility criteria were: (a) any original articles about imported monkeypox; (b) all types of study designs; (c) no restriction regarding the year of publication. The exclusion criteria were: (a) non-human, in-vitro studies; (b) articles in languages other than English; (c) conference papers, abstracts only, author response, books, and reviews and (d) articles with inadequate or overlapping data.

After removing duplicates, an initial screening of titles and abstracts of selected articles was carried out by two authors independently. Next, two independent authors were assigned to screen the full texts. Any conflicts were resolved through discussion and consensus among authors. The first author was consulted if there was any disagreement.

2.3. Case definition

Cases of monkeypox were confirmed by the presence of monkeypox virus deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) testing, next-generation sequencing of a clinical specimen, or isolation of monkeypox virus in culture from a clinical specimen. Imported monkeypox was confirmed when cases reported a history of traveling, within 21 days of illness onset, to a country with confirmed cases of monkeypox or where monkeypox is endemic. Clinically, monkeypox cases had a characteristic rash (i.e., deep-seated and well-circumscribed lesions, often with central umbilication; and lesion progression through specific sequential stages; macules, papules, vesicles, pustules, and scabs) [16].

2.4. Data extraction

Essential data was extracted from the eligible articles including characteristics of participants (age, gender, occupation, suspected source of infection, mode of transmission, diagnosis, infection control measures, management, complications, and outcome) in addition to study characteristics (i.e., authors, year of publication, country, and study design).

2.5. Quality assessment

The quality of the articles was evaluated independently by two authors and was added to the data extraction sheet. The findings of the quality assessment of eligible articles were compared. In case of inconsistent findings, a consensus was reached through discussion and consulting the first author. The Joanna Briggs Institute (JBI) critical appraisal checklist was used for case report studies. The JBI checklist consists of 8 items with four responses (yes, no, unclear, and not applicable)[17]. The quality of case series studies was assessed by National Heart, Lung, and Blood Institute (NIH) quality assessment tool. Studies were classified into good (7−9), fair (4−6) and poor (0−3).[18] The Newcastle-Ottawa Scale (NOS) was used for observational studies. Studies assessed by NOS were categorized as good, fair and poor [19]. (Supplementary File).

3. Results

3.1. Search results

A total of 1886 articles were retrieved using the search strategies. We found 880 citations in 4 databases (WOS, PubMed Central/Medline, and EMBASE), 1000 citations in Google scholar, 4 citations in grey literature, and 2 citations through manual search. We excluded 215 studies as duplicates detected by endnote and 1616 studies during screening by title and abstract. After full-text screening, thirty-four full-text articles were excluded for reasons [duplicates (5), not relevant (13), not-imported monkeypox cases(14), full-text were not-available (1), results not-available (1)]. Of these, 20 studies were included in the systematic review. Additionally, 1 eligible article were found through manual search. Fig. 1.

3.2. Quality assessments

After assessing the quality of the studies, we found 15 studies with good quality [8,10,20–32]. Six studies were of fair quality [8,33–37]. Table 1.

3.3. Study characteristics

Eighteen studies were case report/series design [8,10,20–28,30,32–34,36,39,38], and three were observational studies as cross-sectional and retrospective [29,31,37]. A total of 316 cases were diagnosed with Monkeypox. Fig. 2 Three hundred and nine patients were adult males; five patients were adult females and two were toddlers. From these patients, one hundred and thirteen cases of them had a history of travel and were infected by imported transmission. Four infected males were in their thirties and human immunodeficiency virus (HIV)-positive [23–25,30]. MSM had been reported in 8 studies [23–25,29,31,32,37,40]. Key characteristics of included studies are listed in Table 1.

3.4. Source and destination of imported infection

Nineteen patients mentioned the travel history from Nigeria [10,20–22,26,27,28,33,34–36]. In two studies, destination was to Israel [21,36], two to Singapore [20,36], three to the USA [27,28,33], and six to the UK [10,22,26,34–36].

Thirty-eight infected cases had travel destinations from Europe to Australia [23], Israel [24], Portugal [31], UK [29], Korea [38], Taiwan [8], and to Italy [32]. Fifty-four cases who traveled from European countries such as; Spain, France, and the Netherlands to the UK were mentioned in one study [37]. A study discussed a case traveling from Germany [8]. A case travelled from the UK to the USA was discussed by one study [25] and another study discussed a case traveling from Portugal to Italy [30].

3.5. The mode of transmission among imported cases

Six studies mentioned the cause of imported infection was contact

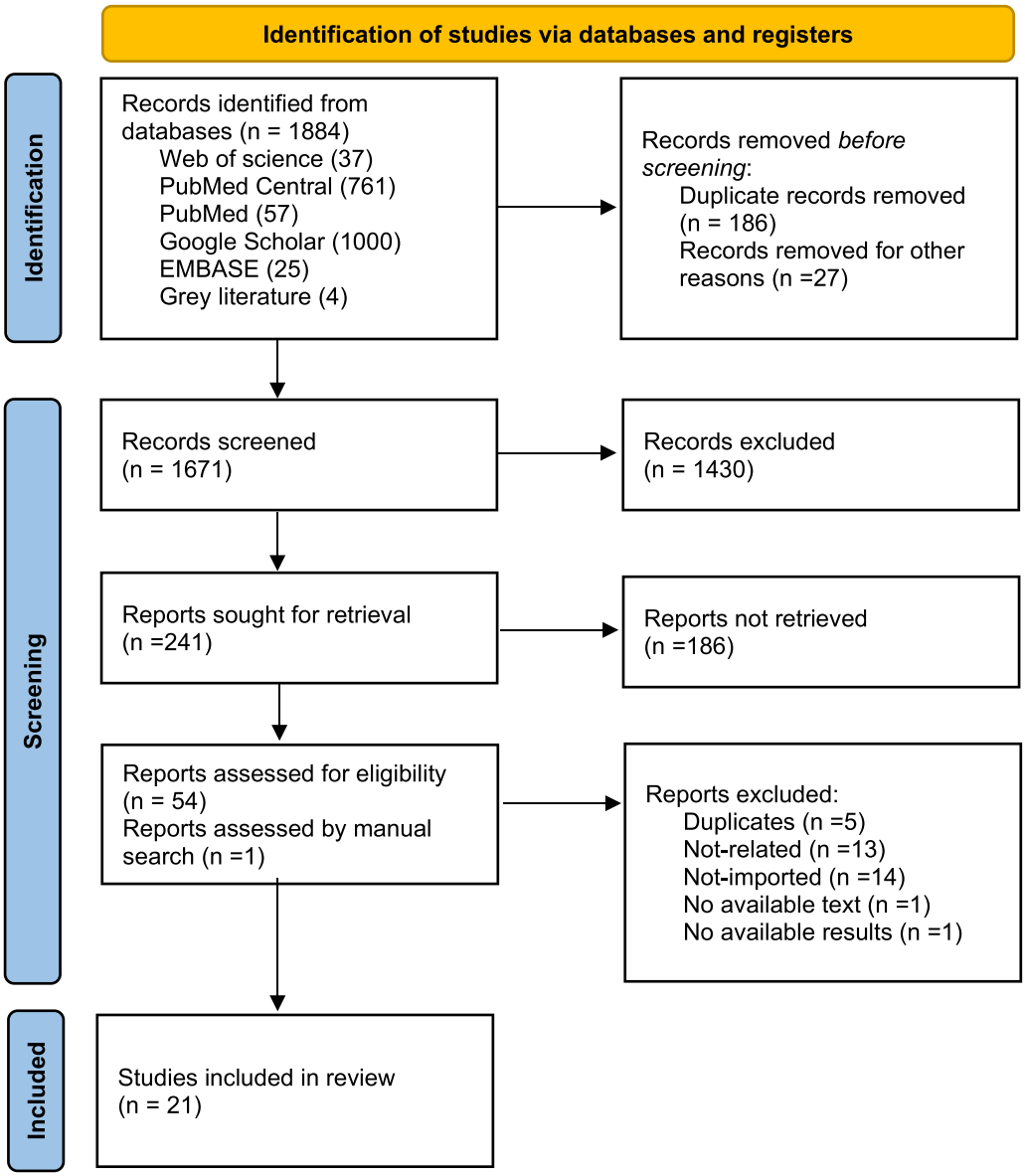

Fig. 1. : Flowchart of included studies.

with an individual with monkeypox symptoms [27,29,33–36]. Two studies discussed cases due to acquired nosocomial infection [10,26]. Ingestion of barbecued bushmeat was the source of infection in three studies [20,34,36] and rodent carcasses were the source of infection in the other two studies [21,28]. Eight studies showed the source of infection was sexual contact, especially with male partners [23–25,30,31,32,37,38]. Figs. 3–4.

3.6. The imported clade of virus and diagnosis

Thirteen studies out of the whole 21 studies reported the virus clade [8,10,20,21,23,27,28,31,32–36]. All reported clades of virus were West African Clades. Diagnosis had been confirmed by PCR [8,10,20,22,24,25,27,29–33,35,37,38,40], genome sequencing [20,34–36,38], Sanger sequencing [31,32], electron microscopy [20,21], and case confirmation [36].

3.7. Clinical signs and symptoms and secondary transmission

Most of the cases had a fever, genital lesion, vesiculopustular rash, headache, lymphadenopathy, night sweats, and chills. Also, gastrointestinal symptoms such as diarrhea and vomiting were presented in some cases[41]. Five studies mentioned that the cases had oral affection [24,25,33,34,38]. Three studies confirmed the presence of secondary transmission between cases [10,35,36].

3.8. Control measures with contacts

Among the 21 included studies, five studies mentioned that vaccination (smallpox\ poxvirus-derived vaccine) of contacts had been offered as post-exposure prophylaxis [20,21,31,34,35]. Also, quarantine and surveillance of these contacts (for the longest incubation period = 21 days from last exposure) were done to control the spread of infection [10,20,21,34,35]. Although two studies mentioned that there was no vaccination offered to the contact, these contacts were not at high risk and they had surveillance and close monitoring [27,33]. Other measures of precautions had been taken as airborne isolation precautions in hospital [23,27,28,33], wearing personal protective equipment (PPE) [20,27,28,31,37]. Home isolation and telephone assessment for patients who were not hospitalized had been reported in two studies [31,37].

Table 1
Studies that addressed cases of Monkeypox across the globe.

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
Erez, 2019 [21]	Medical Center, Israel (Case report)	male - 38 years Desk job (1)	Nigeria	Contact with rodent carcasses	Fever, chills, generalized rash, genital lesion, Lymphadenopathy None None	Electron microscopy, PCR Test, immunofluorescence assay, tissue culture, ELISA	West African	–	NSAIDs, Penicillin, and Doxycycline	Isolated in his residence Only 1\11 HCW agreed to be vaccinated and none of the household contacts agreed	Recovered	7
Yong, 2020 [20]	Tan Tock Seng Hospital emergency department, Singapore (Case report)	Male - 38 years Administrative job (1)	Nigeria	Ingestion of barbecued bushmeat	Fever, chills, myalgia, rash, genital lesion, vesiculopustular rash, Lymphadenopathy None None	PCR Test, Electron microscopy, sequencing	West African	–	–	Isolated in a negative-pressure room in hospital Contacts received vaccine Quarantine of close contacts at home or a government facility Contact tracing Monitoring of HCWs and use of PPE	Discharged	7
Costello, 2022 [33]	A hospital, USA (Case report)	Male −28 years - (1)	Nigeria	Human contact in Nigeria	Skin burning, sensation, vesicular rash, oral affection, lymphadenopathy None	Viral culture, RT-PCR	West African	–	Acyclovir as empiric treatment for disseminated varicella zoster infection	Contact and airborne isolation precautions Surveillance of HCWs	–	6
Atkinson, 2022 [22]	Specialist infectious disease hospital, UK (Case report)	Male - 40 years - (1)	Nigeria	unknown	Fever, generalized pustular rash, genital lesions None -	Orthopoxvirus-specific RT- PCR, MPXV-specific assay	–	–	–	–	–	7
Vaughan, 2018 [34]	Accident and Emergency department at Blackpool Teaching Hospital, UK (Case report)	Males Case 1: Naval officer Case 2: not mentioned (2)	Nigeria	Case 1: - Case 2: Contact with a monkeypox suspected case, ingestion of bush meat	Fever, rash, lymphadenopathy, oral affection, scrotal lump - None	Multiple molecular assays and sequencing analysis	West African	–	Case 1: antibiotics for staphylococcal infections Case 2: antibiotics	Isolated in hospital PEP (vaccine) for contacts PrEP(vaccine) for HCWs Active surveillance for high\ intermediate risk of exposure Passive surveillance for low risk of exposure Contacts received an information sheet about MPXV Contact tracing	Stable and improving	5

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Table 1 (*continued*)

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
Hobson, 2021 [35]	A hospital, UK Emergency department of COVID-19 zone (Case report)	Male - female - toddler 18 months (same family) - (1)	Nigeria	Case 1: (index case) Unknown, Case 2: direct contact (secondary case), Case 3: direct contact (tertiary case)	Vesicular lesions 1 secondary + 1 tertiary cases within the family of the index case) None	PCR Test and sequencing	West African	None	–	Isolated in hospital HCWs in the HCID Unit were offered vaccination Active surveillance for close contacts Passive surveillance for contacts at lower risk of exposure Decontaminat-ion of residence COVID-19 travel quarantine limited MPXV transmission Control measures in the ED	All recovered	4
Hammerschlag, 2022 [23]	A primary care clinic, Australia (Case report)	HIV-positive male in 30 s - on ART - MSM - history of syphilis - (1)	Europe	Sexual contact (MSM)	Rash, painless pustules that became painful and pruritic lesions, fever, malaise, lymphadenopathy - Complications: super imposed infection\ bacterial cellulitis of the penile shaft and lower abdomen	Genome sequencing, Phylogenetic analysis, Electron microscopy	West African	–	Ceftriaxone and Doxycycline for gonorrhea and chlamydia, Cephalexin for superimposed bacterial cellulitis and Cephazolin, Analgesia	Contact and airborne isolation precautions in a room with negative pressure ventilation	Improved and discharged	7
Adler, 2022 [10]	HICD centers, UK (Case series)	4 males - 3 females - age 30–40 + 40–50 + <2 years - all patients were diagnosed from August 2018 to September 2021 and managed in (HCID) centers in Liverpool, London, and Newcastle, coordinated via a national HCID network A HCW - the rest, not mentioned (4)	Nigeria, UK	Imported, nosocomial, and household transmission	Fever, night sweats, lymphadenopathy, groin swelling, coryzal illness, headache, lesions 1 secondary (the toddler) + 1 tertiary case (the HCW) within the family of the index case Side effects: elevated liver enzymes due to brincidofovir, conjunctivitis, and contact dermatitis from cleaning products Complications: Low mood, emotional lability, ulcerated inguinal lesion with delayed healing,	PCR Test for Monkeypox	West African	Only the HCW case (as PEP) due to contact with a secondary case (toddler)	Brincidofovir (3 cases) Tecovirimat (1 case) Opiate analgesia (For neuralgia), azithromycin, ophthalmic chloramphenicol	Isolation 3 siblings (contacts of infected father) were isolated (post-exposure isolation)	All recovered 1 mild relapse	9

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Table 1 (*continued*)

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
					neuralgia, deep tissue abscesses, severe pain, and pruritis							
Patalon, 2022 [24]	Emergency room of a hospital, Israel (Case report)	in 30 s - normal BMI - MSM - case 1 HIV positive - hemorrhoids - case 2 had VTE history - both had a history of Condyloma Acuminatum and were administered the HPV vaccine - (2)	Europe	Sexual contact with infected male partners (MSM)	Fever, muscle aches, fatigue, headache, lymphadenopathy, chills, lesions, oral commissure affection, dyschezia, anal pain, pruritis, high anxiety level, dysuria case 1: no close contacts, case 2: not mentioned None	PCR Test	–	None	Topical antibiotics, analgesics, antihistamine, and Oxycodone	Case 1: isolation Case 2: not mentioned	Recovered with no hospitalization	7
Mauldin, 2020 [36]	Hospitals in UK, Israel, Singapore, and Nigeria (Case series)	Individuals traveling from Nigeria to UK (UK1, UK2) + to Israel (ISR) + to Singapore (SING)+ 1 HCW in UK (UK3) + a case from Bayelsa State (BAY) in Nigeria - 5 males and a female not mentioned for 4 cases and 2 HCWs (4)	Nigeria	UK1: unknown, UK2: ingestion of bushmeat and contact with monkeypox cases, UK3: a HCW, a secondary case (contact with UK2) ISR: contact with rodent carcasses, SING: ingestion of bush meat, BAY: HCW (occupational transmission)	Presence of lesions, fever prodrome UK3 (secondary case) of UK2 (index case) -	Case confirmation, sequencing tests	West African	–	–	–	–	6
Martínez, 2022 [25]	Healthcare setting, USA (Case report)	Male - 36 years - MSM - on HIV as PEP - (1)	UK	MSM (one of sexual contact traveled from the UK to the USA)	No fever, night sweats, sore throat, enlarged tonsils, lymphadenopathy, lesions, oropharyngeal erythema, satellite lesions - Complications: bacterial superinfection \ superimposed cellulitis (on nipples)	Real-time PCR, MPX confirmation by CDC	–	–	IM penicillin G Benzathine, Chlamydia treatment, Empiric gonorrhea therapy with Doxycycline and Ceftriaxone, Amoxicillin/ Clavulanate for superimposed cellulitis	Isolation (not in a hospital)	Recovered	7
Rao, 2022 [27]	Emergency department, USA (Case report)	Early middle-aged male - (1)	Nigeria	Contact with people in a large social gathering in Nigeria	Diarrhea, vomiting, fever, cough, fatigue, purulent rash, pustules None -	Real-time PCR for orthopoxviruses, species-specific RT-PCR at CDC	West African	None	Tecovirimat	Airborne and contact isolation precautions Monitoring of contacts at low \uncertain and intermediate risk of exposure, no persons were at high risk Disinfection of	Discharged (after severe disease)	7

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Table 1 (*continued*)

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
										contaminated surfaces in the airport, two cars used by the case, and his home Mask use during the ongoing COVID-19 pandemic limited transmission of MPXV		
Kunasekaran, 2019 [26]	Royal Liverpool Hospital, UK (Case report)	Case1: Nigerian male resident living at a naval base in Cornwall – Case 2: male resident – case 3: female, 40 years - all in the UK not mentioned for cases 1 and 2- case 3, a nurse (2)	Nigeria	Unknown for cases 1 and 2 (index cases), case 3 (nurse - secondary case), contact with case 2 "nosocomial infection\ occupational transmission"	Rash, headache, swelling of lymph node, back pain, myalgia, fatigue, vesicles pustules None -	–	–	–	Not mentioned for cases 1 and 2 Case 3: not specified	isolation of case1 and 2, not mentioned Case 3 was isolated at a specialist unit at an infirmary follow up of close contacts after their last contact with cases	–	9
Deresinski, 2022 [28]	Emergency department, USA (Case report)	Male - (1)	Nigeria	unknown, maybe from urban areas in Nigeria	Cough, fever, diarrhea, and vomiting then, a purulent skin eruption None -	–	West African	None	Tecovirimat	Airborne and contact isolation precautions Monitoring of contacts Disinfection of planes between flights and patient's homes Mask use during the ongoing COVID-19 pandemic limited transmission of MPXV	Discharged	8
Patel, 2022 [29]	A regional HCID, UK (Retrospective study)	Median age 38 years - males - 196\197 were gay, bisexual, or MSM - 35.9% had HIV- other STIs, gonorrhea for Chlamydia trachomatis, herpes simplex virus, and Treponema pallidum. Inclusion criteria: All confirmed cases between 13 May and 1 July 2022 - (54)	Western Europe: Spain, France, Belgium, Germany, and Greece + West Africa	Contact with monkeypox cases, travel to Western Europe, travel to West Africa, sexual contact with males (majority of cases)	Lesions, fever, rash, pruritis, myalgia, lymphadenopathy, rectal pain, penile swelling - complications: abscesses, urinary retention, superimposed bacterial lower RTI, disseminated lesions severe rectal pain and perforation, proctitis, necrotizing secondary bacterial infection (ex. Streptococcus	PCR Test for MPXV	–	–	Antibiotics, Metronidazole and Tecovirimat (some cases), Antibiotics for superadded infections, Analgesics, Opioids, Lidocaine gel, oral laxatives, Fentanyl for severe rectal pain, Co-amoxiclav for bacterial infection, Ceftriaxone and Metronidazole for	Isolated in hospital, and in containment facilities	All improved	7

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Table 1 (*continued*)

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
					pyogenes), paraphimosis or phimosis, solitary cutaneous lesion				procitis and other drugs			
Mileto, 2022 [30]	A clinic, Italy (Case report)	Italian male living in Portugal - 33 years - HIV infection - fully vaccinated against COVID-19 - (1)	Portugal	Sexual contact with a casual partner in Lisbon \ Portugal	Asthenia, malaise, anorexia, lesions, pharyngodynia, sneezing, fever, lymphadenopathy - None	Non-human orthopoxvirus Testing, Real-time PCR for MPXV	–	–	–	Isolated in a negative-pressure room in a hospital Isolation after discharge until lesions recovered	Mild disease - remained well till discharge	7
Girometti, 2022 [37]	Open-access sexual health clinics, UK (Retrospective study)	MSM - 4% bisexual- median age is 41 years (IQR 34 –45)- 70% were White, 15% Black or mixed race, 7% Asian, 7% other ethnicities - 48% were born in the UK, 25% had concomitant STIs, 24% had HIV Inclusion criteria: all lab-confirmed cases between May 14 and May 25, 2022 - (25)	European countries: Spain, France, and Netherlands	MSM 94% and 46% of individuals traveled outside UK (88% of individuals who reported location of travel, reported visits to European countries)	Fatigue, lethargy, fever, skin lesion, lymphadenopathy - Complications: pain, localized bacterial cellulitis mainly on the penile site	RT-PCR assay with clade-specific PCR	–	–	Ceftriaxone and Doxycycline for bacterial cellulitis, Metronidazole, Tecovirimat (1 case) Analgesics	Hospital isolation, Isolation and telephone assessment for patients not hospitalized PPE for HCWs, fit-tested FFP3 respirators No mixing in waiting rooms	All clinically improved and discharged	5
Perez Duque, 2022 [31]	Healthcare facilities, Portugal (Observational study)	MSM - median age 33 years (range: 22–51) - Almost all cases live in Lisbon and Tagus Valley health region - more than 50% had HIV Inclusion criteria: confirmed cases with the earliest symptom onset on 29 April - (4)	Europe	Contact with a monkeypox confirmed case, travel abroad (ex. UK), sexual contact with men (1 case with only women) most cases had sex with multiple partners, and contact with animals (cats and pigs)	Exanthema, lymphadenopathy, fever, Asthenia, headache, genital ulcers, vesicles - None	RT-PCR, Sanger sequencing, viral clade identification	West African	One case was vaccinated	–	Home isolation Exclusion of work (sick leave) Hospital isolation (3 cases) Self-monitoring of contacts Contact tracing was difficult Contact precautions Hand hygiene PPE Risk communication and social mobilization to reduce transmission	3 Hospitalized cases Discharged (2 of them) No severe cases	7
Yang, 2022 [8]	Taiwan Center for Disease Control, Taiwan (Case report)	Male - 20 years student (1)	Germany	–	Fever, sore throat, muscle pain, lymph node swelling in groin, rash, atypical skin lesion - -	PCR Test, Phylogenetic analysis	West African	None	–	Close contacts were quarantined	–	7

(*continued on next page*)

Table 1 (*continued*)

Author Year [Ref]	Study setting Study design	Population Criteria Job (Number of imported cases)	Source	The suspected source of infection \ mode of transmission	Signs and symptoms Secondary cases complications \ side effects	Diagnosis	Clade of virus	Vaccination history (poxvirus-derived vaccine)	Treatment	Control measures	Outcome	Quality score
Jang, 2022 [38]	Incheon Medical Center, Korea (Case report)	Male - 34 years – bisexual - (1)	Germany	MSM with suspected monkeypox infection partner	Penile ulcer, headache, fever, sore throat, perioral erosive lesion, rash - -	RT-PCR for MPXV, gene sequencing	–	–	–	Isolated at the airport, then at Incheon Medical Center	–	5
Antinori, 2022 [32]	Two different hospitals in central Italy, Italy (Case report)	Males - in the 30 s - MSM - history of STIs as syphilis - cases 1 and 3 had HIV and received effective ART; cases 2 and 4 were on PrEP - (4)	Gran Canary island (in Spain)	MSM	Skin lesions, lymphadenopathy, fever, asthenia, itchy papules, myalgia - None	RT-PCR for MPXV, Sanger sequencing	West African	Case 3, vaccinated during childhood	Case 1: Ciprofloxacin, Acyclovir and Benzylpenicillin case 2: Anti-inflammatory and Antihistaminic medications cases 3 and 4: not mentioned	Isolation in hospitals Droplet and contact isolation measures plus filter face piece-2 (FFP2)	All were in good clinical condition and recovered spontaneously	8

Active surveillance for high and intermediate risk exposure and passive surveillance for low risk of exposure [34,35]. Quarantine for forward-traced contacts was done to control the spread of infection [20, 35,40].

4. Discussion

In this review, we aimed to trace the cases of imported monkeypox reported worldwide to identify the source of infection and destination of these cases for early control infection. We included 21 studies; the quality of included studies was good except of six studies. A total of 316 cases were infected with monkeypox; three hundred and nine patients were adult males, five patients were adult females, and two toddlers. One hundred and thirteen cases were infected by imported monkeypox. The cases were confirmed by PCR, genome sequencing, Sanger sequencing, electron microscopy, and clinical signs and symptoms. Fortunately, in this review, all cases reported were of the West African clade, the less severe form.

The advance of globalization, frequent personnel exchanges and close international trade cooperation make it possible for infectious diseases from all over the world to be imported resulting in modification of certain diseases epidemiology [39]. Mobile populations may modify the epidemiology of certain infectious diseases in the world as they can introduce new infections that in the presence of a viable vector could produce outbreaks in the host country or reintroduce previously eradicated infections [42]. Usually, health care workers, in these areas, are not familiar with such conditions. In fact, there are numerous examples of failed control programs, not the least of which is the increased rate of tuberculosis in developed countries, which is concentrated in specific populations such as immigrants and refugees [43]. Imported malaria is claimed to have led to resurgences of the disease in previously eliminated areas such as Zanzibar, as well as in previously eliminated nations such as Greece and Turkmenistan.[44–46] Other examples are imported vaccine-preventable diseases that are seen as individual cases or small outbreaks among immigrants and other mobile populations. Previously, almost all cases of monkeypox in people outside of Africa were attributed to international travel to countries where the disease was common or to imported animals [47]. Recent evidence of the role of travel in increasing the risk of infection was provided by large case series conducted across 16 countries including 528 cases. Travel was the second reported risk factor (20%) after sex (28%) in acquiring monkeypox [48]. In this review, we found that about one-half of the studies reported imported cases from Nigeria. Africa and Asia were the main origins of imported malaria and other mosquito-borne diseases [49,50]. First, because of the rapid development of international economic exchange, trade, and travel, the number of migrant workers from Africa increased dramatically. Second, climate and sanitary conditions in Africa and Southeast Asia are suitable for mosquitoes and other vector survival. In fact, international travel witnessed a marvelous recovery after lifting measures on international travel to contain coronavirus disease (COVID-19). According to the latest United Nations World Tourism Organization World Tourism Barometer, international tourism saw a strong rebound in the first five months of 2022, with almost 250 million international arrivals recorded. This compares to 77 million arrivals from January to May 2021 and means that the sector has recovered almost half (46%) of pre-pandemic 2019 levels. In Africa and the Middle East, arrivals could reach about 50–70% of pre-pandemic levels [51]. However, they have been described as carrying significant infectious disease burdens, determined by geographic origin, ethnicity, health conditions at the departure point, and the migratory route [52,53]. It is worth noting that, many of these infections may be asymptomatic for long periods [54].

In the current work, nine studies reported association between sexual contact especially MSM and infection with monkeypox. Indeed, people of any race/ethnicity, gender, gender identity, sexual orientation, or other traits can contract monkeypox through specific behaviors.

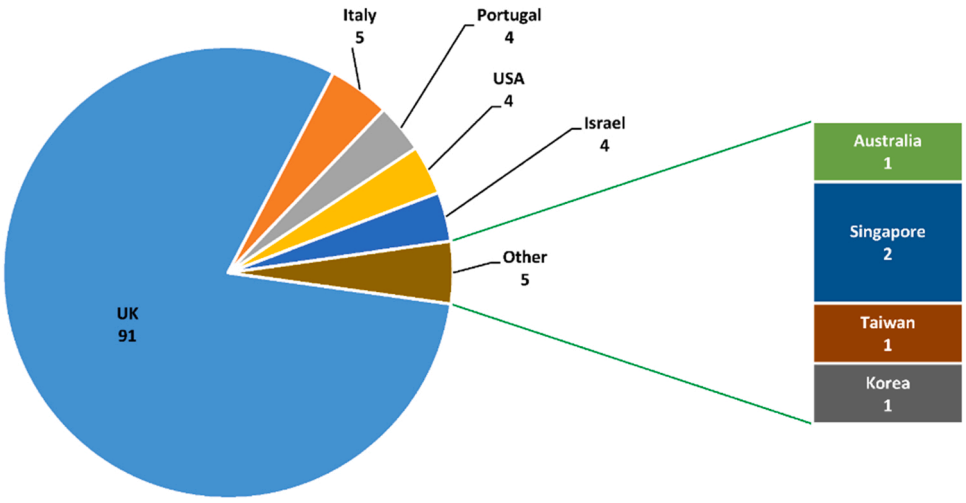

Fig. 2. : Number of monkeypox cases registered in different countries with travel history.

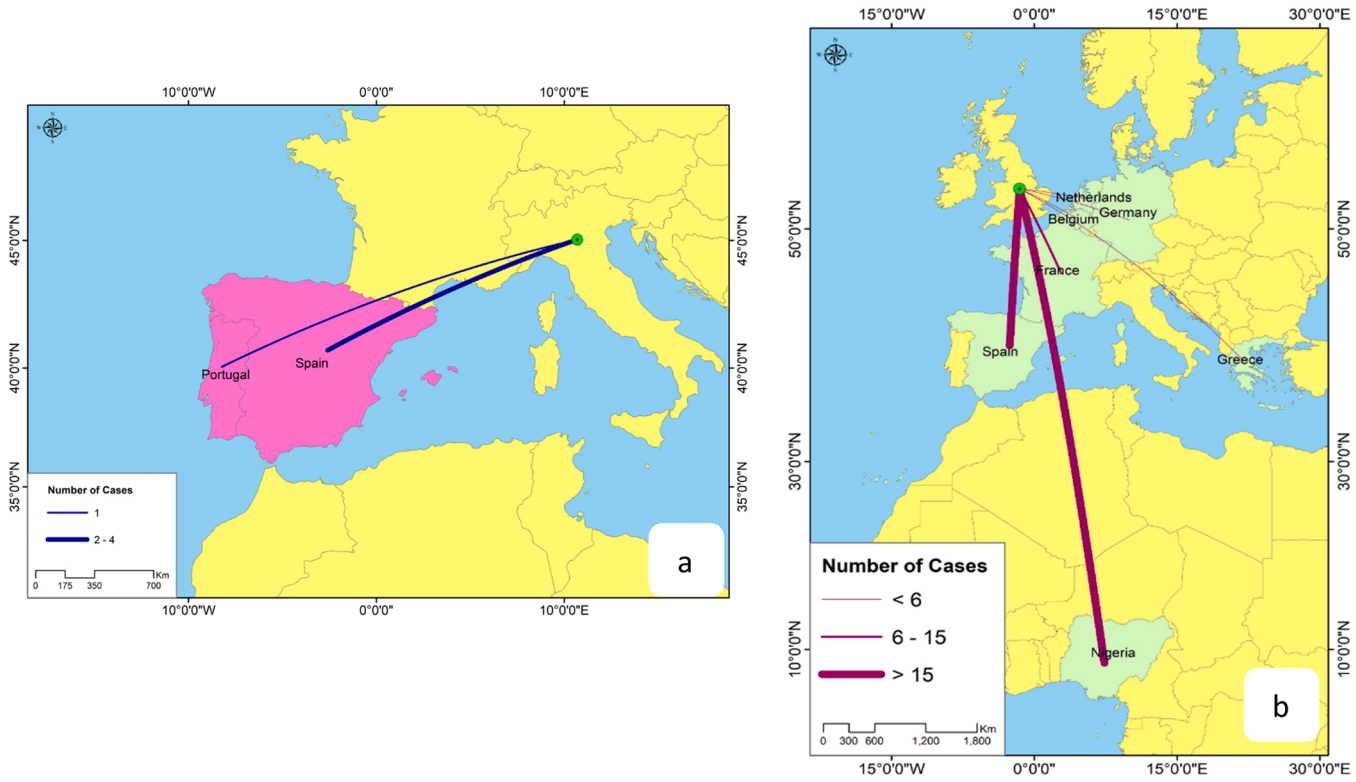

Fig.: 3. (a) Number of monkeypox cases traveled to Italy from different origin 3(b) Number of monkeypox cases traveled to United Kingdom from different origin.

Homosexual, bisexual, and MSM account for most infections in the current outbreak.[55] So, health message and distribution tactics may need to be tailored to reach these people directly, such as through particular websites, dating applications, or media programs. Messages should be explicit and nonjudgmental, and any sexual activity should not be stigmatized.

In this review, the preventive measures implemented by the countries that reported imported cases varied from case isolation, vaccination, decontamination, and active surveillance. This may urge the need for development of effective standardized control plan that should be put in place for countries to prevent further diseases spread. This plan should focus on case finding, contact tracing, laboratory investigation, isolation, immunization, and case management may be implemented through communicable disease surveillance system.[56] This surveillance has two main functions: early notification of potentially transmissible diseases, and monitoring. The value of these surveillance systems is their ability to detect an unusual number of transmissible infections (e.g., an outbreak of dengue), generate an alert, and lead to the communication of this outbreak to the public health authorities to take actions to control the main source of infection, and thus prevent further spread. Timely dissemination of surveillance results can improve the planning, implementation, and evaluation of public health practice. For an efficient surveillance system, public and private health physicians need to continually review their efficiency in detecting and treating imported monkeypox. At the same time, the personnel working at different levels of surveillance need to report data quickly and accurately to ensure rapid and effective actions against possible infectious disease outbreaks.[43] Another crucial measure of imported monkey

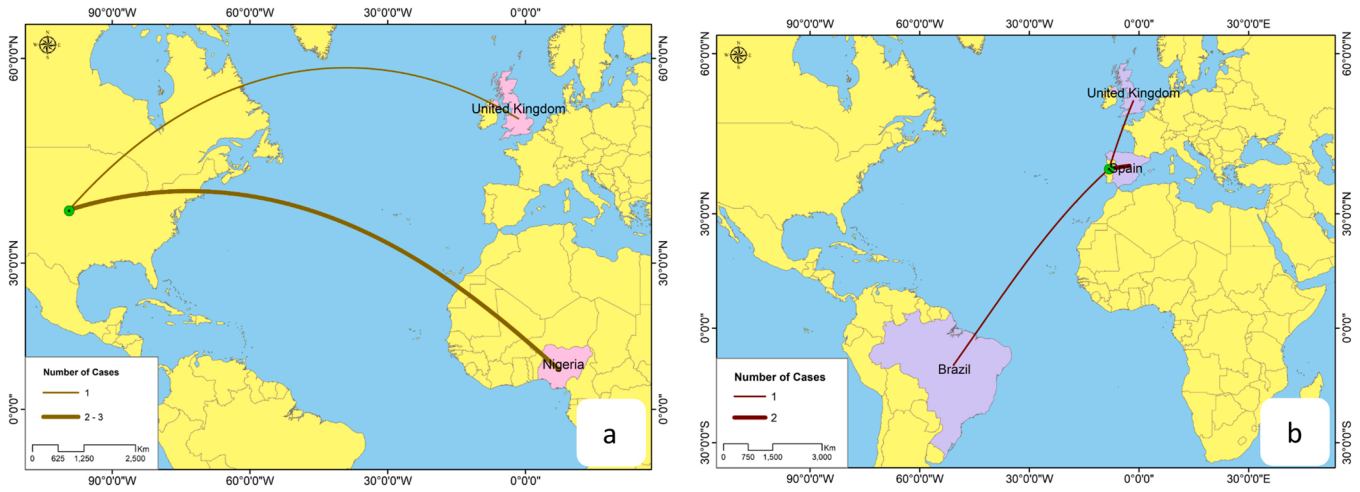

Fig.: 4. (a) Number of Monkeypox cases traveled to USA from different origin. 4(b) Number of Monkeypox cases traveled to Portugal from different origin.

pox is points of entry screening. The WHO advised that health promotion and risk communication materials be accessible at points of entry, including information on how to detect signs and symptoms associated with monkeypox, prevent its spread, and seek medical care at the destination if necessary.[56].

4.1. Strengths and limitations

To the best of our knowledge, this is the first study to shed light on imported monkeypox. This study will pave the way for future studies that may help in a better understanding of disease epidemiology. In this study, different databases were searched in addition to grey literature. However, published studies are scarce, and most of the included studies were either case reports or case series that would provide weak evidence and hinders external validation of the study findings. Also, some observational studies could include cases which already could be reported by previous case studies.

5. Conclusion

Identifying and treating imported monkeypox could result in a benefit both for the individual concerned and for public health. Development of functioning surveillance system of communicable diseases is now, because of globalization, a key function for worldwide health security. This system necessitates ongoing training of front-line health professionals to ensure that monkeypox is properly recognized and diagnosed and all cases are promptly reported, and that all cases are investigated to determine whether the infection was acquired locally or abroad. In addition, implementing effective health communication about monkeypox prevention and control is mandatory to help individuals to make informed decisions to protect their own and their communities' health.

Author contribution

RMG, the conceptualization of research idea, writing the manuscript, database search; responded to reviewers' comments. EMH, screening of articles; MAH, screening of articles; AM, writing manuscript, data extraction; SZ, data extraction; EHE, writing manuscript, quality assessment; NF, quality assessment, writing manuscript, SAA, article screening; RE, data extraction; HMH, protocol writing and registration; AHS, manual search; HHAA, database search; NR, database search; HA, search strategy, submission; EE, search strategy; MAH, writing manuscript, EAH, grey literature search, writing manuscript; MH, contributed to the conceptualization of research idea, writing the manuscript, and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work. All authors read and approved the manuscript. All authors declare no conflict of interest.

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Conflict of interest

We have no disclosures. We do not have conflicts of interest associated with this publication. This manuscript is original, has not been previously published, and is not currently under consideration by another journal.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.cimid.2022.101923.

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